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Olfaction in migraine

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Olfactory thresholds for acetone and vanillin and the unpleasantness rating of concentrated acetone were measured in 20 migraine sufferers and 21 controls. The olfactory threshold for vanillin was lower in migraine sufferers than in controls. In addition, patients who reported that odours frequently seemed stronger during attacks of migraine were able to detect acetone, at a lower concentration than most other patients. No differences were found between migraine sufferers and controls for ratings of the unpleasantness of concentrated acetone. These findings suggest that hyperacuity to odours persists between episodes of migraine. Sensitivity to odours could contribute to the migraine predisposition. *Migraine, olfaction, sensory hyperacuity, trigeminal nerve*

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Sensitivity to light, noise and smells often increases during migraine; normal room lighting appears glarey and painful, the slightest sound is heard clearly, and innocuous odours become offensive (1). This sensitivity could result from loss of normal inhibitory controls during headache, so that trivial sensory experiences cause discomfort and aggravate the headache. Persistence of this disturbance could increase the predisposition for migraine. For example, sensitivity to glare persists between episodes of headache (2, 3), and intense or flashing lights apparently trigger some attacks (4). Hearing thresholds and auditory discomfort thresholds are normal during the headache-free interval (5), but auditory sensitivity may persist between attacks in patients who attribute their headaches to loud noise (4).

Strong odours may trigger attacks of migraine (4, 6), sensitivity to odours and olfactory hallucinations sometimes develop during migraine (7–10), and headaches attributed to diet might involve olfaction. Despite these circumstantial links, little is known about olfaction in migraine. For example, olfactory thresholds in migraine apparently have been investiated in only one study (11). In this report, olfactory thresholds to pyridine were elevated in 12 of 67 migraine sufferers (18%), compared with an expected rate of anosmia (loss of olfactory sensation) of about 1% in the normal population of the United States (11). Unfortunately, the effect of the testing

protocol on olfactory thresholds could not be determined in this study because thresholds were not measured in normal controls. Since a random order of four differing concentrations of pyridine was used, olfactory adaptation could have developed if strong odours preceded weak odours (12). Furthermore, pyridine is not a pure olfactory stimulus because it also stimulates trigeminal nerve endings in the nasal mucosa; in fact, the trigeminal sensation induced by pyridine can be detected by people with anosmia (13).

Strong stimulation of trigeminal nociceptors in the nasal mucosa evokes tickling, stinging, burning, hot or cold sensations, and induces protective responses such as secretion of mucus, engorgement of intra-nasal erectlie tissue and changes in respiration. At weaker stimulus intensities, the trigeminal system interacts with the olfactory system both at the central level and peripherally to influence the perception of odours (14). Most odours are capable of trigeminal stimulation, low concentrations of vanillin apparently being one of the few exceptions (13).

The aim of the present study was to investigate the olfactory and trigeminal perception of odours in a sample of migraine sufferers studied during the headache-free interval. It was hypothesized that the odour of acetone, which stimulates the trigeminal and olfactory nerves, would be detected more easily by migraine sufferers than by controls. For comparison, the odour of vanillin was used as a pure olfactory stimulus. In addition, ratings of unpleasantness to a suprathreshold stimulus (concentrated acetone) were obtained. It was hypothesized that the odour of acetone would be more unpleasant for migraine sufferers than controls.

Methods

Subjects

The migraine sample consisted of 17 females and 3 males aged between 15 and 57 years (mean age 36 years) who met the International Headache Society criteria (15) for migraine without aura (13 patients) or migraine with aura (7 patients). Patients were matched with 18 females and 3 males aged between 19 and 56 years (mean age 33 years) who reported fewer than eight headaches per year, none with symptoms of migraine. Four migraine sufferers and three controls were smokers. Nine patients (three of

[Fig. 1.]

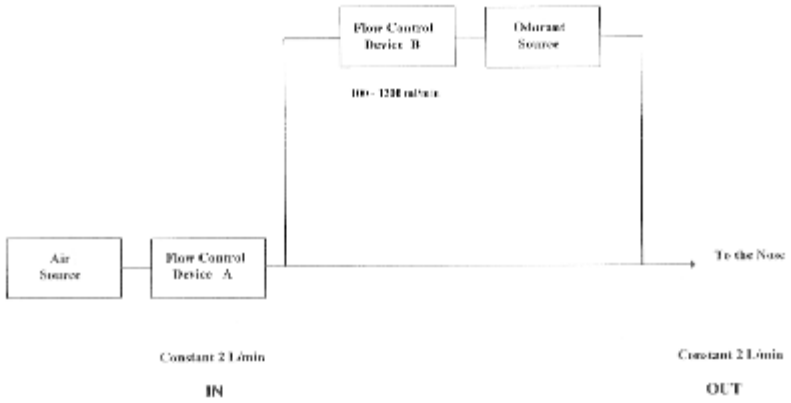

Fig. 1. Devices used to regulate air flow. Compressed air was regulated to arrive at the nose at 2 L/min. A low-flow regulator controlled the proportion of air that was diverted through a vanillin or acetone solution, up to a maximum of 1,200 ml/min.

them smokers) reported that smells frequently seemed stronger during their attacks. Seven patients reported that headaches were precipitated by aromatic foods such as cheese or chocolate, but only one patient thought that odours induced migraine. Headaches recurred at least once per month in 17 patients and every 6–8 weeks in the other three patients (mean frequency 23 headaches/year). Eleven patients reported that at least 70% of attacks recurred on the same side of the head.

All subjects gave their informed consent and were paid Australian $10 for participating. The experiment was approved by the Murdoch University Ethics committee.

Procedure

Fresh solutions of vanillin and acetone were prepared daily by dissolving 2 gm of vanillin in 100 ml of distilled water, and 100 µl of acetone in 100 ml of distilled water. The subject sat in a comfortable chair in a well-ventilated room maintained at 22±1ºC. At the start of each trial the subject held a 4 mm diameter disposable tube which released medical air at 2 L/min just inside their right or left nostril. The subject was informed that the first trial would start soon, and was asked to signal when he noticed the vanillin odour. The subject was told that the smell "will seem to waft in and you will think 'Is that it?' This is when I want you to tell me that you can smell it. The smell never gets very strong." About 5 min later, the experimenter began to adjust a low–flow meter so that the proportion of odorant in the medical air increased but the output to the nostril remained at 2 L/min (Fig. 1). The proportion of air flow through the vanillin solution increased at a rate of 500–600 ml/min until the vanillin odour was detected, or to a maximum of 1,200 ml/min. Flow through the vanillin solution was maintained at 1,200 ml/min for 1 min and then the procedure was repeated for the other nostril. To prevent adaptation, each nostril was tested only once. The entire procedure was then repeated with the dilute acetone solution, using separate tubing to avoid any possibility of contamination between the acetone and vanillin.

Next, the subject was instructed to block either the left or right nostril and to breathe in for the count of three, while a 5 ml vial of acetone was held under the unblocked nostril. The subject was asked to rate the odour on a 10-point scale, with one corresponding to "extremely pleasant" and 10 to "extremely unpleasant". This

procedure was repeated for the other nostril.

Results

Preliminary analyses indicated that olfactory thresholds and ratings of unpleasantness did not differ between the left and right nostrils in the control group, and were similar on the two sides in most cases [all paired *t*-tests were non-significant; Pearson's correlation coefficient for vanillin, $r(18)=0.81$, $p<0.001$; for acetone, $r(19)= 0.82$, $p<0.001$; for unpleasantness ratings, $r(19)=0.65$, $p<0.001$]. Furthermore, neither olfactory thresholds nor ratings differed between the symptomatic and non-symptomatic sides in patients with unilateral migraine. For these reasons, we chose to define the olfactory thresholds for each solution as the lower of the values obtained for the left and right nostrils, and used the highest unpleasantness rating as the best estimate of sensitivity to concentrated acetone.

Two migraine sufferers and five controls who could not detect the odour of vanillin with either nostril were assigned an arbitrary threshold of 1,200 ml/min (the maximum flow rate through the vanillin solution). All but two migraine sufferers were able to detect the odour of dilute acetone with at least one nostril. One of these patients was unable to detect the odour of vanillin or dilute acetone with either nostril, but was able to detect the odour of concentrated acetone. All of the control subjects detected the odour of dilute acetone with at least one nostril. Differences in olfactory thresholds and ratings between migraine with aura, migraine without aura and control subjects were investigated in analyses of variance, with orthogonal planned contrasts between the migraine and control groups and between the two migraine categories. As shown in Fig. 2, the olfactory threshold for vanillin was lower in migraine sufferers than in controls [$t(36)=2.16$, $p<0.05$], but did not differ significantly between the two migraine categories. Neither the olfactory threshold for dilute acetone nor the unpleasantness rating for concentrated acetone differed among the three groups (Fig. 2). However, Fig. 3 shows that olfactory thresholds for dilute acetone were consistently low in patients who reported that odours frequently seemed stronger during migraine, whereas thresholds were far more variable in patients who had rarely or never noticed this symptom [mean flow rate±SD, 396±35 ml/min versus 621±332 ml/min; Levene's test for equality of variance, $F= 10.9$, $p<0.01$; *t*-test adjusted for unequal variances, $t(10.3)=2.23$, $p<0.05$]. Olfactory thresholds for vanillin and unpleasantness ratings for concentrated acetone were unrelated to odour sensitivity during migraine.

Discussion

Migraine sufferers were able to detect vanillin at a weaker concentration than control subjects. This finding contrasts with those of Hirsch (11), who concluded that migraine sufferers had considerably poorer odour detection thresholds than the general population. Hirsch suggested that diagnostic error, medication effects or the use of a forced-choice paradigm might have contributed to the high rate of anosmia in his migraine sample; in addition, presenting strong before weak stimuli probably

provoked olfactory adaptation and an artificial elevation of the olfactory threshold in some cases (12).

Vanillin stimulates olfactory receptors but not trigeminal nociceptors, at least in the concentrations used in the present study (13). Nasal or sinus disease, exposure to toxins, head trauma, prior upper respiratory tract infection and many systemic diseases can compromise odour sensitivity (16); some of these diseases also distort the perception of odours or produce olfactory hallucinations (17), but are unlikely actually to improve odour sensitivity. The basis of odour hyperacuity in the present sample of migraine sufferers is uncertain, but is consistent with

[Fig. 2.]

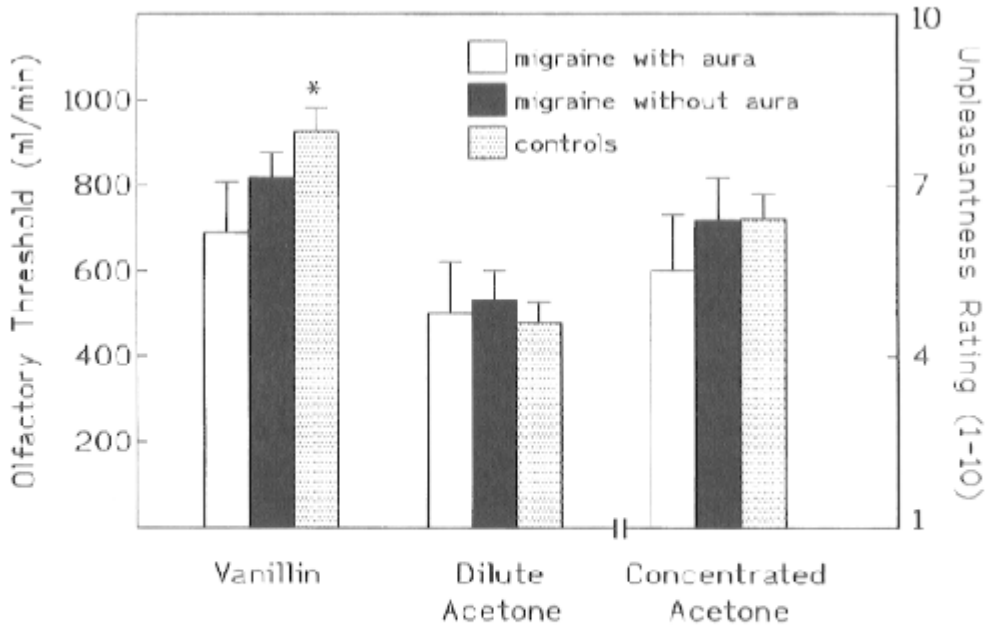

Fig. 2. Olfactory thresholds for vanillin and dilute acetone, and unpleasantness ratings for concentrated acetone. The olfactory threshold for vanillin was lower in migraine sufferers than in controls ($^{*}p<0.05$). Bars represent the standard error of responses.

[Fig. 3.]

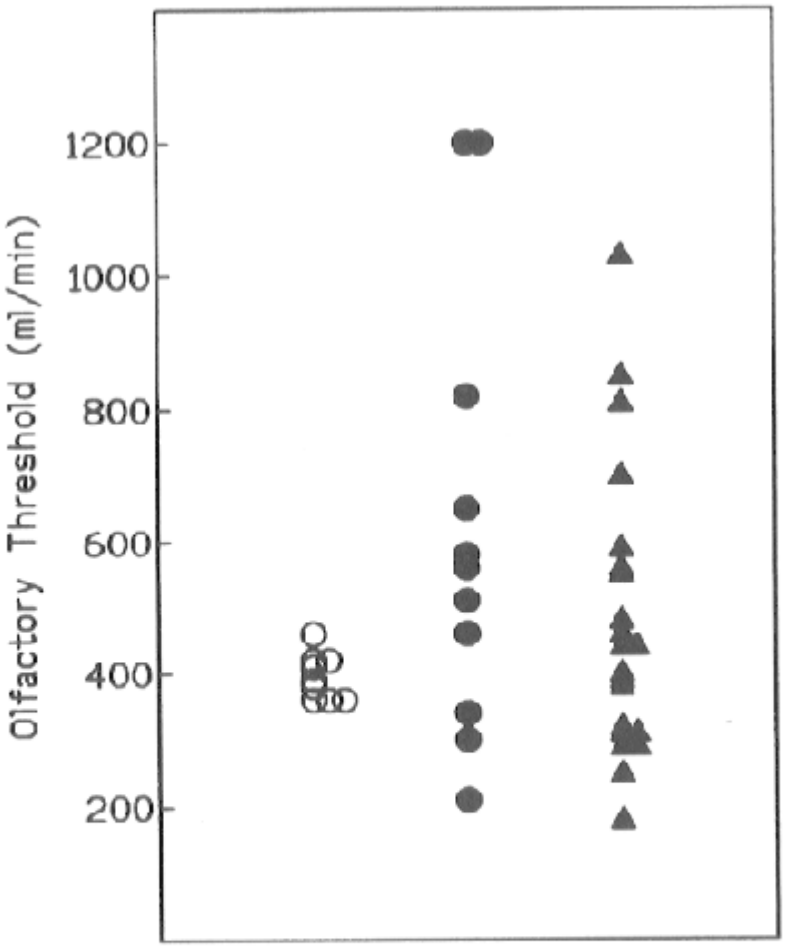

Fig. 3. Olfactory threshold for dilute acetone, presented individually for each subject. The olfactory threshold was less variable and, on average, lower in patients who had noticed that odours frequently seemed stronger during migraine than in the remainder of patients. ○=Olfactory sensitivity during migraine; ●=migraine without olfactory sensitivity; ▲=controls.

the notion of a persistent low-grade sensory hyperacuity of the olfactory system that intensifies during attacks of migraine, in parallel with sensitivity to light and noise (1).

Patients who reported that odours frequently seemed stronger during attacks of migraine detected dilute acetone at a lower concentration than most other migraine sufferers. The detection threshold for vanillin, a pure olfactory stimulant, was unrelated to odour sensitivity during migraine. Thus, the findings suggest an association between odour sensitivity during migraine and trigeminal hyperacuity during the headache-free interval. This speculative hypothesis needs to be tested on a new sample of patients

with various trigeminal stimulants. Trigeminal hyperacuity apparently does not affect the perception of suprathreshold stimuli, because ratings of unpleasantness of the odour of concentrated acetone were similar in migraine sufferers and controls.

Unlike the other cranial nerves, the cell bodies of the olfactory nerve lie within the structure of the brain. This anatomical arrangement permits toxins and viruses taken up by the olfactory nerve to be transported retrogradely to the dorsal raphe nuclei and locus coeruleus (18), which interact closely with the trigeminovascular system (19). Perhaps olfactory migraine develops as an attempt to interrupt the entry of toxins into the brain, or to expel accumulated toxins arriving by this route.

In summary, the findings suggest that residual sensitivity of the olfactory nerve and nasal branches of the trigeminal nerve persists between episodes of headache. This residual sensitivity might increase susceptibility to migraine (3, 20).

References

1. Lance Jw. Mechanism and management of headaches, 4th ed. London: Butterworths, 1982
2. Drummond PD. A quantitative assessment of photophoibia in migraine and tension headache. Headache 1986;26:465–4
3. Drummond PD, Woodhouse A. Painful stimulation of the forehead increases photophobia in migraine sufferers. Cephalalgia 1993;13:321–4
4. Debney LM. Visual stimuli as migraine trigger factors.In: Clifford Rose F, editor. Progress in migraine research, vol II. Pitman Press: Bath, 1984:30–54
5. Woodhouse A, Drummond PD. Mechanisms of increased sensitivity to noise and light in migraine headache. Cephalalgia 1993;13:417–21
6. Scharff L, Turk DC, Marcus DA. Triggers of headache episodes and coping responses of headache diagnostic groups. Headache 1995;35:397–403
7. Wolberg FL, Ziegler DK. Olfactory hallucinations in migraine. Arch Neurol 1982;39:382
8. Blau JN, Solomon F. Smell and other sensory disturbances in migraine. J Neurol 1985;232:275–6
9. Crosley C, Dhamoon S. Migrainous olfactory aura in a family. Arch Neurol 1983;40:459
10. Ardila A, Sanchez E. Neuropsychological symptoms in the migraine syndrome. Cephalalgia 1988;8:67–70
11. Hirsch AR. Olfaction in migraineurs. Headache 1991;37:233–6
12. Cometto-Muniz JE, Cain WS. Olfactory adaptation. In: Doty RL, editor. Handbook of olfaction and gustation. New York: Marcel Dekker, 1995:257–81
13. Dory RL, Brugger WE, Jurs PC, et al. Intranasal trigeminal stimulation from odorous volatiles: psychometric responses from anosmic and normal humans. Physiol Behav 1978;20: 175–85
14. Doty RL. Intranasal trigeminal chemoreception: anatomy, physiology and psychophysics. In: Doty RL, editor Handbook of olfaction and gustation. New York: Marcel Dekker, 1995: 821–33
15. Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Cephalalgia 1988 Suppl 7
16. Duncan HJ, Smith DV. Clinical disorders of olfaction: a review. In: Dory RL,

editor. Handbook of olfaction and gustation. New York: Marcel Dekker, 1995:345–65
17. Leopold D. Distorted olfactory perception. In: Dory RL, editor. Handbook of olfaction and gustation. New York: Marcel Dekker, 1995:441–54
18. Baker H. Transport phenomena within the olfactory system. In: Dory RL, editor. Handbook of olfaction and gustation. New York: Marcel Dekker, 1995:173–90
19. Lance JW, Lambert GA, Goadsby PJ, Duckworth JW. Brain-stem influences on the cephalic circulation: experimental data from cat and monkey of relevance to the mechanism of migraine. Headache 1983;23:258–65
20. Drummond PD. Sweating and vascular responses in the face: normal regulation and dysfunction in migraine, cluster headache and harlequin syndrome. Clin Autonom Res 1994;4:273–85